Needs for NIT Development to Reduce Misclassification of Non-Responders in Clinical Trials

NASH Liver Forum 12

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Boehringer Ingelheim

Disclaimer

- Judith Ertle is an employee of Boehringer Ingelheim
- All stated opinions in this presentation are the presenter´s opinions and are not reflecting Boehringer Ingelheim´s position

My First Thoughts on Non-Responders

- *… or better questions*

- *What do we define as response?*
- *How to develop and validate biomarkers?*

- *Do we need just better compounds?*

Treatment Response

How do we define treatment response?

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Improvement in Long-Term Outcomes are the Ultimate Goal of Treatment in NASH

- The ultimate goal of NASH treatment is to slow the progress of, halt, or reverse disease progression and improve clinical outcomes (i.e., prevent progression to cirrhosis and cirrhosis complications, reduce the need for liver transplantation, and improve survival).

- Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival …
- Resolution of steatohepatitis on overall histopathological reading **and** no worsening of liver fibrosis on NASH CRN fibrosis score. …

OR (FDA) // AND (EMA)

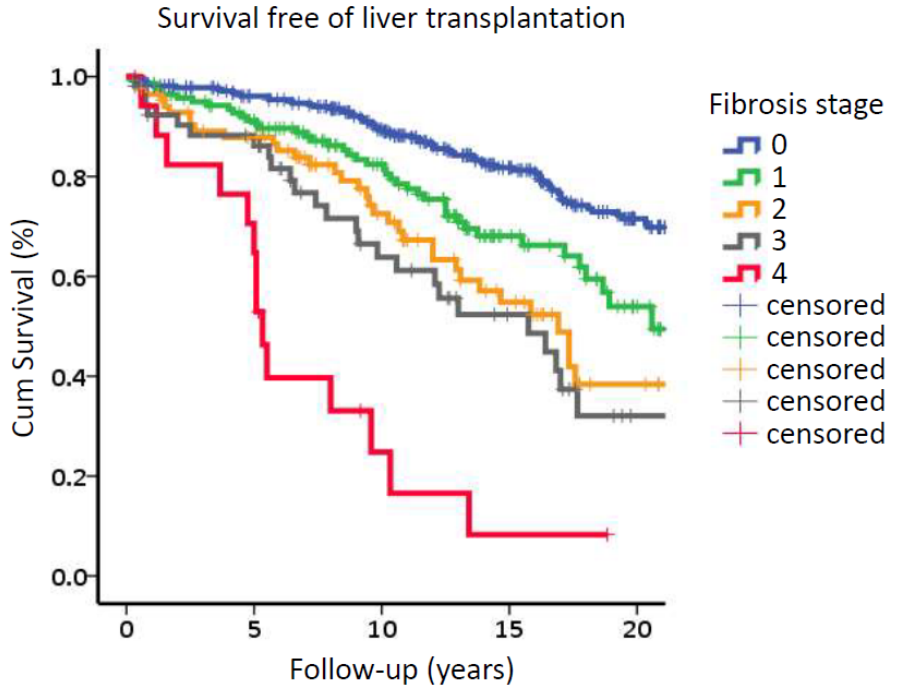
- Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) **and** no worsening of steatohepatitis

Draft Guidance
Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment
Guidance for Industry

Liver Fibrosis, but no Other Histologic Features, Associates with Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

B2.2 Development of Cirrhosis as Potential Surrogate Endpoint for NASH Clinical Trials: There is a body of data that supports that the development of histologically identified cirrhosis predicts a significant worsening of health status.

Sanyal et al., Hepatology, 2015



Angulo et al., Gastroenterology, 2016

- Liver histology as surrogate endpoint to support accelerated/conditional approval of noncirrhotic NASH

FDA Webinar 2021

Non-responders

Are non-responders misclassified or just non-responders?

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Responders and Non-Responders are Classified by Histological Outcomes

REGENERATE Trial

- Reporting of histological improvement and worsening of fibrosis stage after 18 months of treatment

Younossi et al., Lancet, 2019

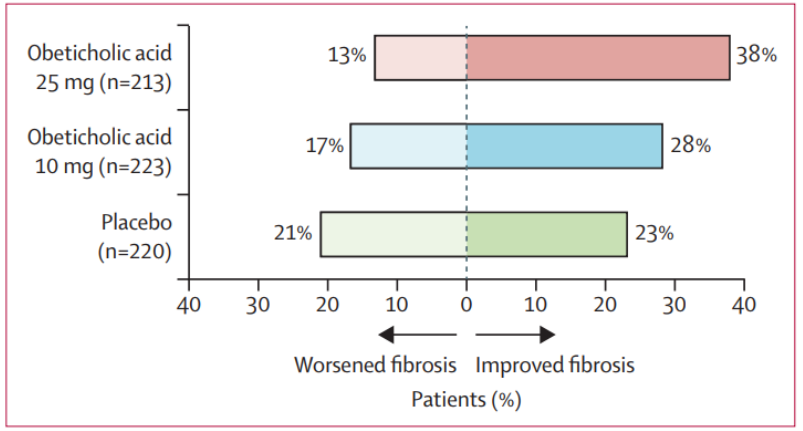
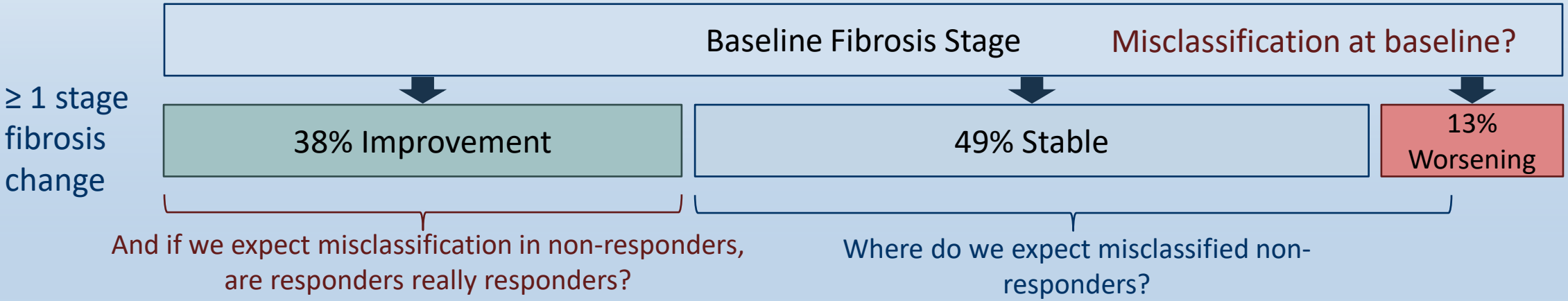
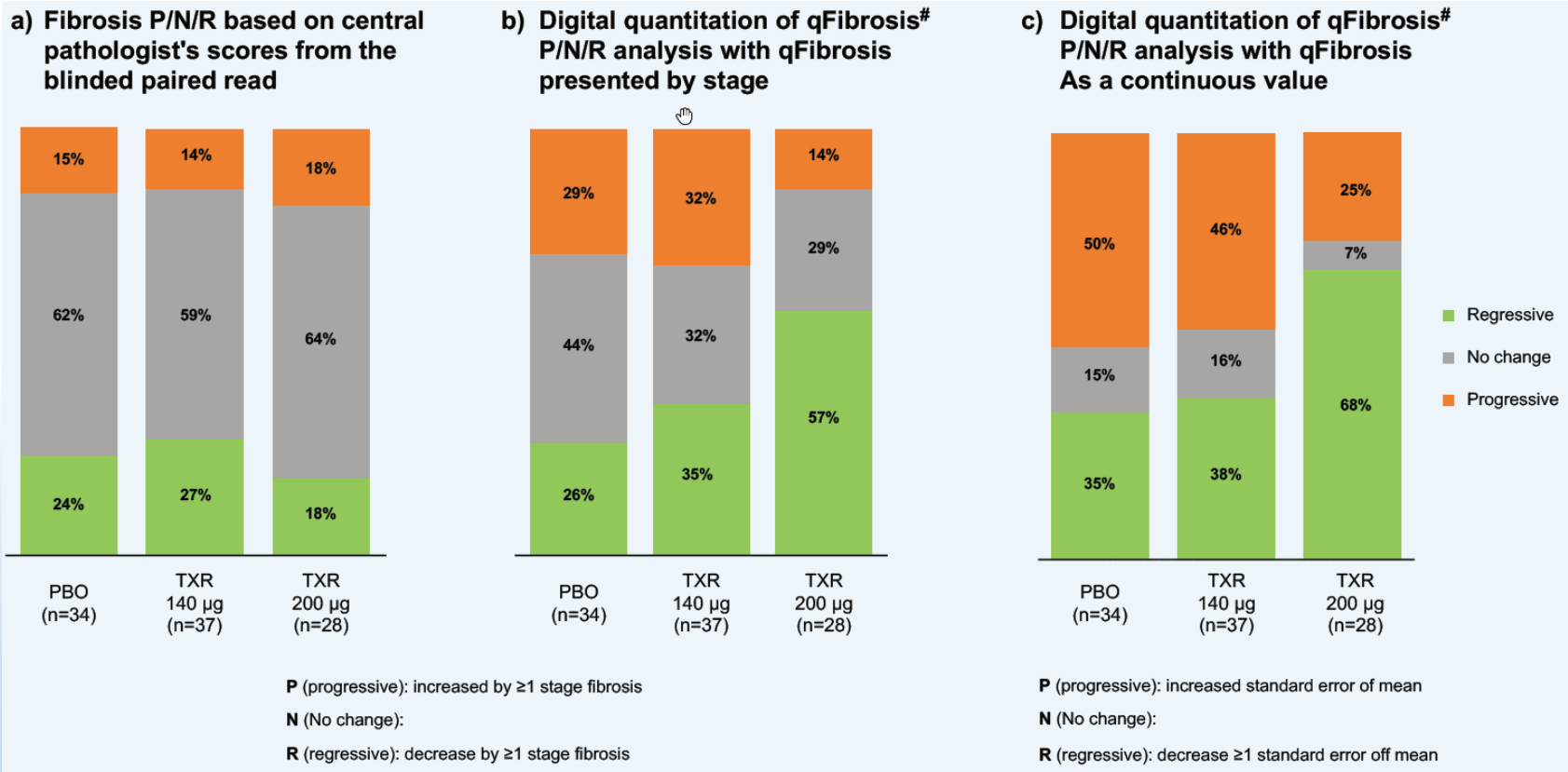


Figure 3: **Regression or progression of fibrosis by at least one stage in the per-protocol population**
The proportion of patients with improved or worsened fibrosis by at least one stage is shown for the 656 patients in the per-protocol population with available fibrosis stage data at month 18 or end of treatment.



Quantitative Fibrosis Assessment improves the Classification of Responders and Non-Responders



Naoumov et al., ILC2021 PO-889

- Quantitative fibrosis assessment provides more granular classification of treatment response
- However, this still requires biopsy, and these classifications are not further established or validated for outcomes

Biopsy vs. NITs

How do we establish/validate NITs?

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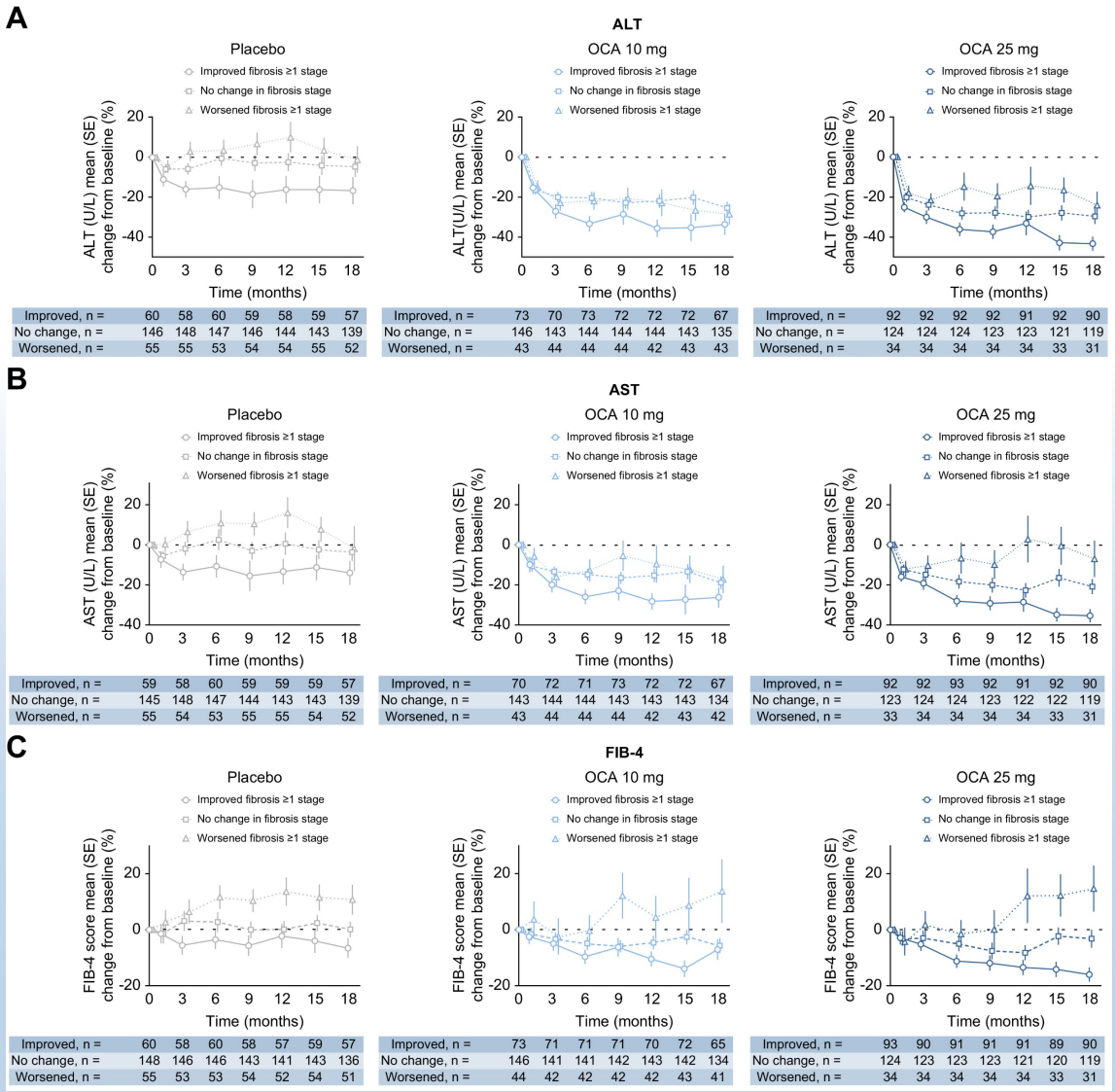
What can we learn from the REGENERATE Trial… 1/3

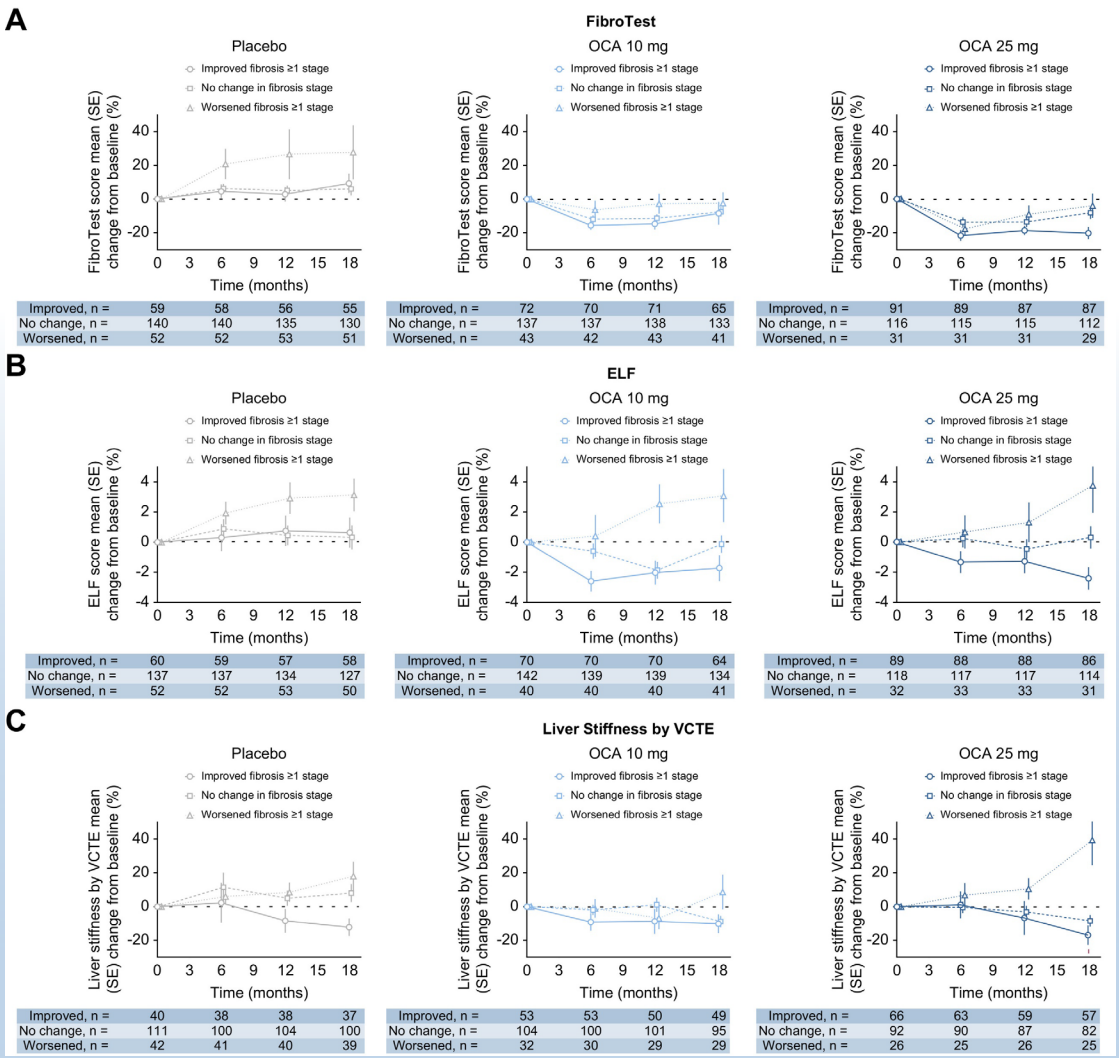
- Transaminases decrease in responders most likely due to MoA of obeticholic acid
- FIB-4 (age, AST, ALT, platelet count) follows fibrosis stage changes



Rinella et al., Journal of Hepatology, 2021

What can we learn from the REGENERATE Trial… 2/3

- Fibrotest (γ-GT, Total bilirubin, Alpha-2-macroglobulin, Apolipoprotein A1, Haptoglobin) seems to reflect MoA
- ELF™ (hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase 1) follows fibrosis changes, however, differentiation might be only detectable after „long“ treatment
  - Pro-C3 did not change → Which factors change and is it fibrosis or MoA?
- Transient Elastography follows fibrosis change, but only with substantial tissue remodeling



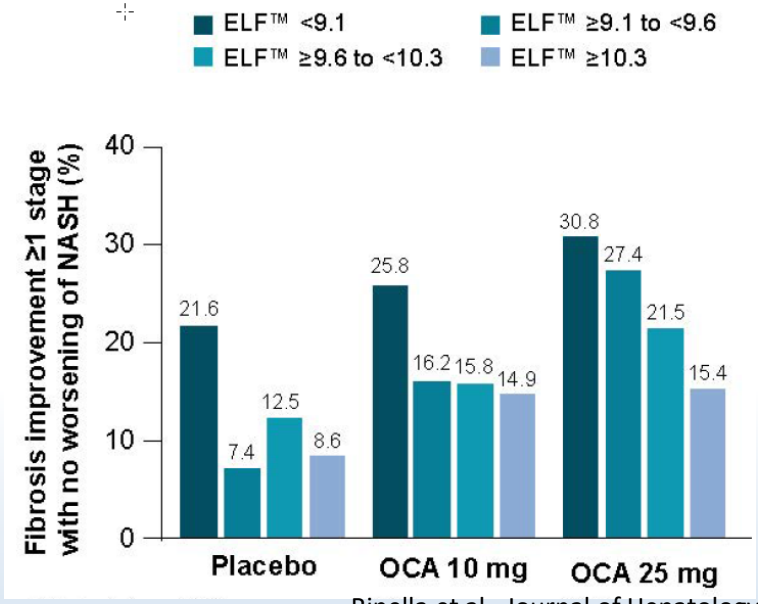
Rinella et al., Journal of Hepatology, 2021

What can we learn from the REGENERATE Trial… 3/3

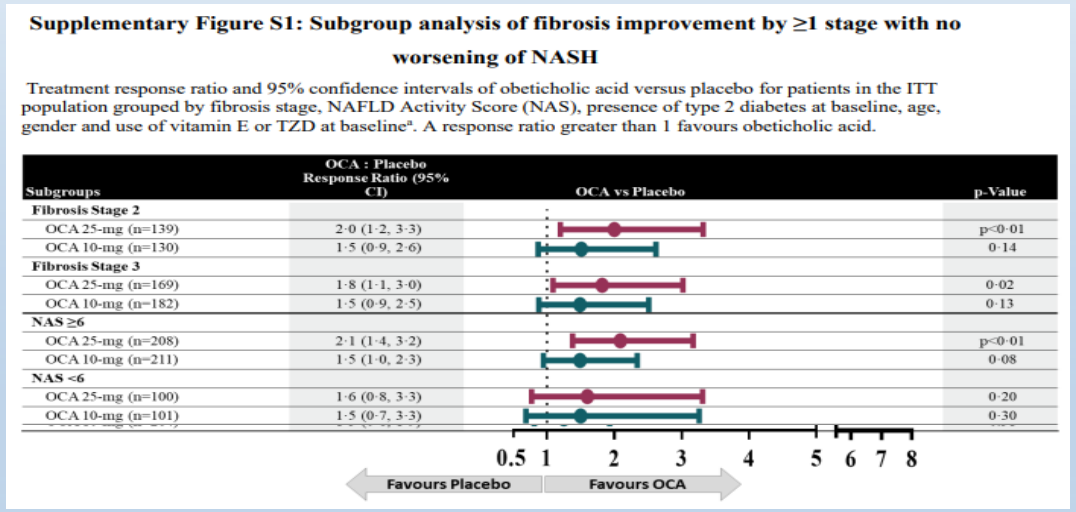
- ELF™ score has shown to be prognostic at point of diagnosis
  - What does change mean?
- Improvement of fibrosis most pronounced in patients with lower ELF score (= earlier patients?)
  - Is that due to MoA?

Most Important Question:

Can we use these insights for other MoAs?



Rinella et al., Journal of Hepatology, 2021



Supplementary Figure S1: Subgroup analysis of fibrosis improvement by ≥1 stage with no worsening of NASH

Treatment response ratio and 95% confidence intervals of obeticholic acid versus placebo for patients in the ITT population grouped by fibrosis stage, NAFLD Activity Score (NAS), presence of type 2 diabetes at baseline, age, gender and use of vitamin E or TZD at baseline[a]. A response ratio greater than 1 favours obeticholic acid.

Subgroups	OCA : Placebo Response Ratio (95% CI)	OCA vs Placebo	p-Value
Fibrosis Stage 2			
OCA 25-mg (n=139)	2·0 (1·2, 3·3)		p<0·01
OCA 10-mg (n=130)	1·5 (0·9, 2·6)		0·14
Fibrosis Stage 3			
OCA 25-mg (n=169)	1·8 (1·1, 3·0)		0·02
OCA 10-mg (n=182)	1·5 (0·9, 2·5)		0·13
NAS ≥6			
OCA 25-mg (n=208)	2·1 (1·4, 3·2)		p<0·01
OCA 10-mg (n=211)	1·5 (1·0, 2·3)		0·08
NAS <6			
OCA 25-mg (n=100)	1·6 (0·8, 3·3)		0·20
OCA 10-mg (n=101)	1·5 (0·7, 3·3)		0·30

Younossi et al., Lancet, 2019

Long-Term Outcomes

How do we establish/validate NITs?

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Improvement in Long-Term Outcomes are the Ultimate Goal of Treatment in NASH

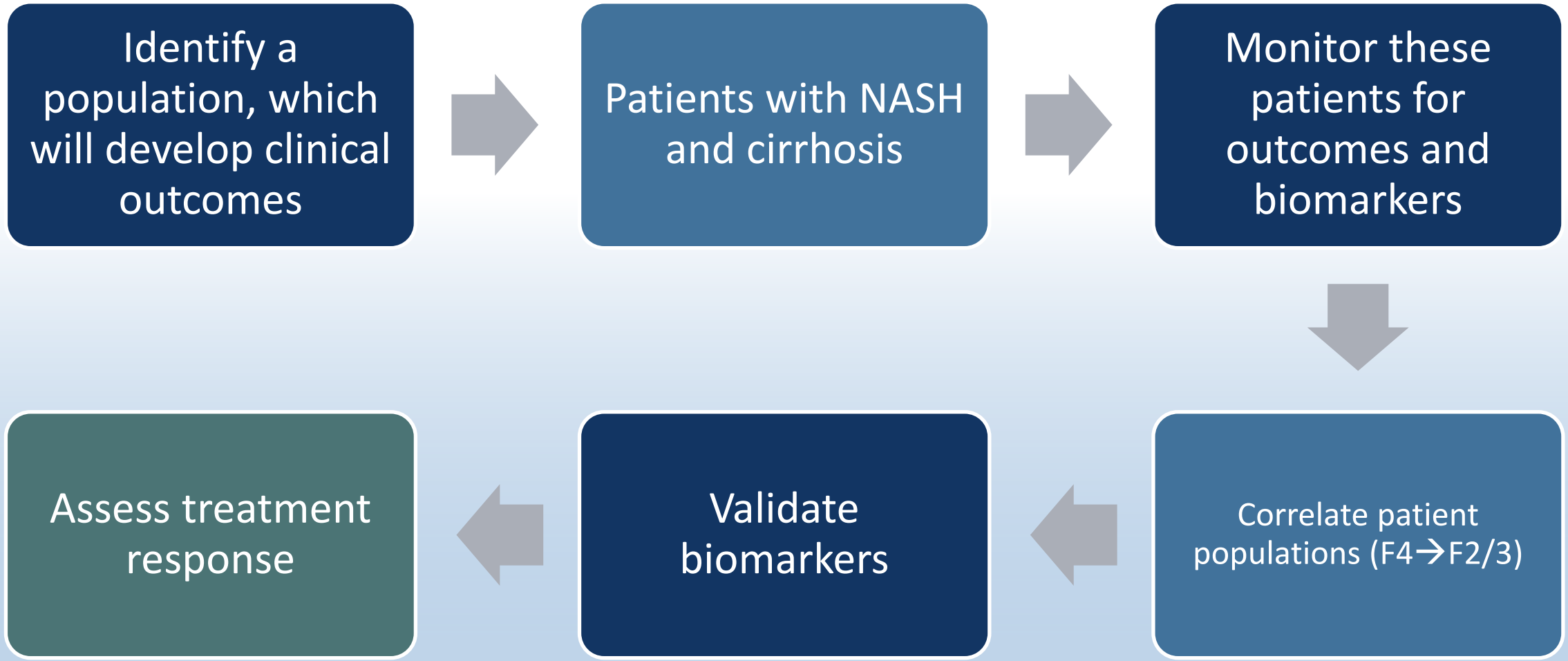
- The ultimate goal of NASH treatment is to slow the progress of, halt, or reverse disease progression and improve clinical outcomes (i.e., prevent progression to cirrhosis and cirrhosis complications, reduce the need for liver transplantation, and improve survival).

- Currently we are mostly identifying and validating *SURROGATES for SURROGATES*

➢ We have to identify, establish and validate biomarkers as surrogate endpoints to clinical outcomes, *NOT* biopsy readouts

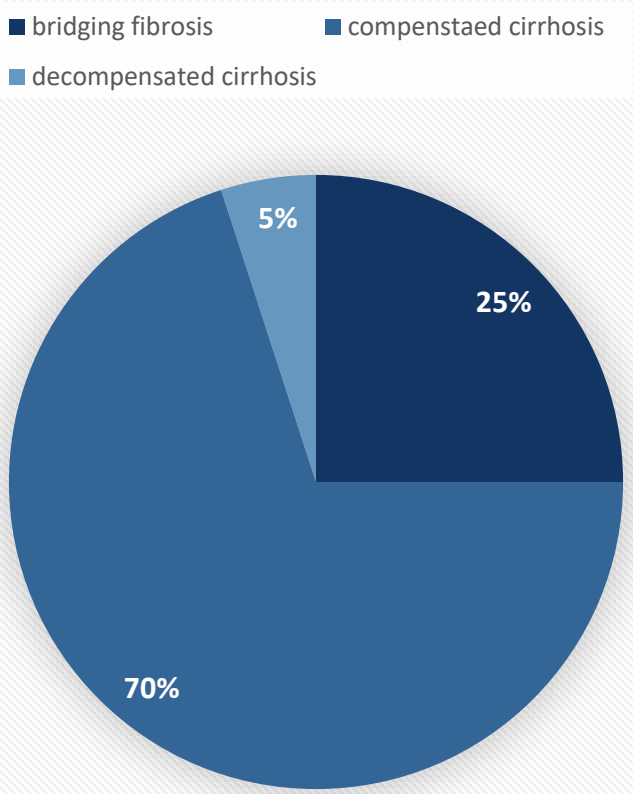
Draft Guidance
Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment
Guidance for Industry

Proposal for Development of NITs in NASH



BI's Non-Drug Minimal-Interventional NASH F4/Cirrhosis Study (NINA-C) in a Nutshell

Patient population at baseline (n=10,000)



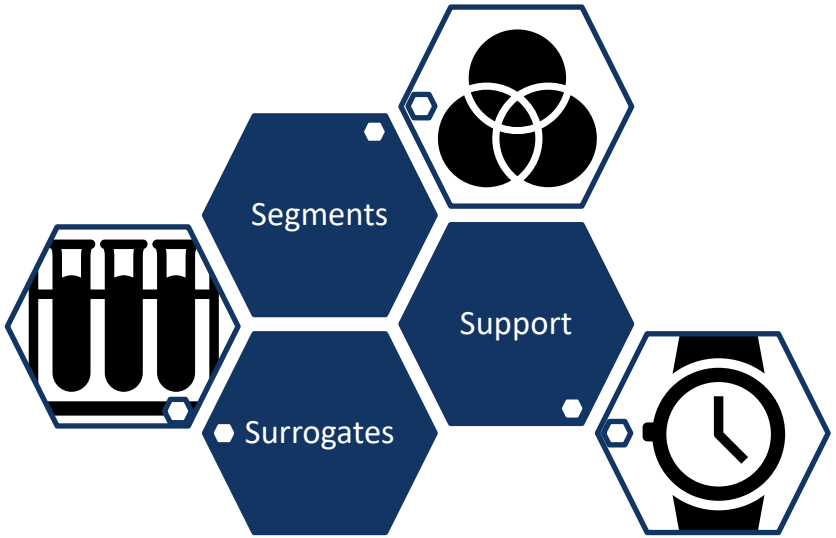
Operational aspects

Global trial

Total trial duration
10 years
Visits every 6 months

Objectives

Correlate biomarkers & clinical data with occurrence of patient outcomes
- Liver related outcome events
- CV outcome events
- All cause mortality



Thank you for your attention!